CONCISE REPORT

Growth and infectious exposure during infancy and the risk of rheumatoid factor in adult life

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Background: The contribution of the environment to rheumatoid arthritis (RA) remains uncertain. Intrauterine and early postnatal life may be important. Rheumatoid factor (RF) found in around 10% of the normal population confers a risk of developing RA and may be present years before onset of clinical disease. The immune pathology leading to RA and RF may have similar genetic and environmental influences.
Objective: To measure RF in people for whom data on birth weight, infant growth, and markers of infectious exposure during infancy and childhood, had been previously recorded.
Methods: 675 men and 668 women aged 59–67 years, born and still resident in Hertfordshire, UK, were studied. RF was measured with an ELISA. Associations between presence of RF, early growth, and markers of hygiene in infancy, were investigated.
Results: RF was detected in 112/675 (16.6%) men and 79/668 (11.8%) women. No significant relationships existed between early growth and presence of RF in men or women. Among women, sharing a bedroom during childhood was associated with a lower risk of RF positivity (OR = 0.48, 95% CI 0.30 to 0.78, p = 0.003).
Conclusions: A developing immune system exposed to increased infectious exposure is less likely to produce RF in adult life; this may reduce the pathological process which leads to RA.

The precise cause of rheumatoid arthritis (RA) is unknown. Disease models suggest that both genetic and environmental factors are important.[1] There has been limited success in defining these environmental factors, perhaps because studies have concentrated on the period around the onset of clinical disease. Recent work has suggested that perinatal characteristics may be important in the development of RA.[2]

Rheumatoid factor (RF) is an autoantibody strongly associated with RA. It is present in up to 10% of the normal population, and its presence confers a risk of developing RA, which increases with higher titres.[3] In addition, RF may be present up to 10 years before the onset of clinical disease.[4]

We suggested that environmental factors important in RA may be acting in utero or early infancy. To investigate this possibility we looked for RF in a population study of subjects with well defined early lives to see whether early growth and markers of infectious exposure were associated with the presence of RF in later life.

PATIENTS AND METHODS

Study population

The Hertfordshire Cohort Study (HCS) includes 3000 men and women born in the county of Hertfordshire, UK, between 1930 and 1939. Midwife and health visitor records have been preserved for the cohort containing information on birth weight, weight at 1 year, method of infant feeding and markers of exposure to childhood infection (sharing a bedroom during childhood, social class (own social class for men and never married women and husband's social class for married women—the social classes used were non-manual (I, II, IIINM) and manual (IIIM, IV, V)), and birth order). People recorded in the ledgers and still living in Hertfordshire were identified from a National Health Service registry and invited to attend a clinic, where serum samples were collected. We included 726 men and 671 women from the first region of Hertfordshire (East Hertfordshire) who had full histories and samples available.

Measurement of RF

RF was measured using an enzyme linked immunosorbent assay (ELISA; INOVA Diagnostics, Inc, San Diego, USA) and a positive result was defined as ⩾6 IU/ml. The level of 6 IU/ml was chosen from the sensitivity of the ELISA and to eliminate false negative results. RF results were obtained for 675 (93%) men and 668 (99.5%) women.

Statistical analysis

We investigated associations between the presence of RF, early growth (birth weight, weight at 1 year, and growth rate), and markers of hygiene (father's social class, sharing a bedroom during childhood, and birth order) in infancy, using cross tabulations and logistic regression models. All analyses were conducted using the Stata statistical software package, release 8.

RESULTS

RF prevalence

A positive RF was present in 112/675 (16.6%) men and 79/668 (11.8%) women. The ages of all subjects studied were between 61 and 69 years when serum samples were taken. RF titres >30 IU/ml were detected in 24 women (3.6% of all women tested) and 29 men (4.3% of all men tested).

Early life size and growth

No significant relationships existed between early life growth (including birth weight, weight at 1 year, and conditional growth rate) and the presence of RF in men or women (tables 1 and 2).

Early life hygiene

No significant relationships existed between markers of infant hygiene and the presence of RF in men (table 1). However, for women sharing a bedroom during childhood

Abbreviations: CCP, cyclic citrullinated peptide; ELISA, enzyme linked immunosorbent assay; HCS, Hertfordshire Cohort Study; RA, rheumatoid arthritis; RF, rheumatoid factor

Table 1 Early life characteristics and RF in Hertfordshire Cohort Study men, n = 675

Characteristic	Frequency	RF +ve cases No (%)	Odds ratio (95% CI) Univariate	Mutually adjusted
Birth weight (g)				
<3175	215	43 (20.0)	1.0	1.0
3175–3629	233	36 (15.5)	0.73 (0.45 to 1.19)	0.76 (0.46 to 1.25)
>3629	227	33 (14.5)	0.68 (0.41 to 1.12)	0.69 (0.41 to 1.15)
			p = 0.26 on 2df	*p = 0.32 on 2df*
Weight at 1 year (g)				
<9752	236	38 (16.1)	1.0	
9752–10575	199	34 (17.1)	1.07 (0.65 to 1.78)	*Not included in model*
>10575	240	40 (16.7)	1.04 (0.64 to 1.69)	
			p = 0.96 on 2df	
Conditional growth				
Lowest third	223	29 (13.0)	1.0	1.0
Middle third	222	41 (18.5)	1.52 (0.90 to 2.54)	1.57 (0.92 to 2.68)
Highest third	230	42 (18.3)	1.49 (0.89 to 2.50)	1.54 (0.90 to 2.63)
			p = 0.22 on 2df	*p = 0.19 on 2df*
Social class (III–V v I–IIINM)				
I–IIINM	107	13 (12.1)	1.0	1.0
IIIM–V	527	91 (17.3)	1.51 (0.81 to 2.81)	1.59 (0.85 to 3.00)
Missing/ unclassified	41	8 (19.5)	1.75 (0.67 to 4.61)	1.73 (0.65 to 4.62)
			p = 0.38 on 2df	*p = 0.33*
*Shared bedroom as child**				
No	294	50 (17.0)	1.0	1.0
Yes	377	62 (16.4)	0.96 (0.64 to 1.44)	1.01 (0.63 to 1.59)
			p = 0.85	*p = 0.98*
Birth order				
1st	262	46 (17.6)	1.0	1.0
2nd–4th	323	49 (15.2)	0.84 (0.54 to 1.30)	0.88 (0.55 to 1.42)
⩾5th	89	17 (19.1)	1.11 (0.60 to 2.05)	1.28 (0.64 to 2.60)
			p = 0.59 on 2df	*p = 0.50 on 2df*

*Four results missing.

was associated with a lower risk of being RF positive (odds ratio = 0.48, 95% confidence interval 0.30 to 0.78, p = 0.003) (table 2). There was also a trend towards low birth order (2nd−5th+) and lower social class (IIIM–V) being associated with a reduced likelihood of being RF positive in women. These results were unaltered in mutually adjusted analyses. We found that the concentration of RF had no effect on our results, although, this analysis was limited by small numbers

DISCUSSION

These results show a significant association between an environmental factor during infancy and the presence of RF in women. Sharing a bedroom during early childhood significantly reduced the likelihood of being RF positive in later life (odds ratio = 0.48, 95% confidence interval 0.30 to 0.78, p = 0.003). There were also trends towards an association of fewer siblings and a higher social class with RF in women. These characteristics have previously been used in studies of other autoimmune diseases, including type I diabetes mellitus and multiple sclerosis, to define infectious exposure.[5 6] Reduced exposure to micro-organisms is thought to result from higher social class, fewer siblings, having your own bedroom during childhood, and living in an urban environment.

The population used has been extensively studied and is very stable over time making it unlikely that subjects moving away from the area will have altered the results. The HCS cohort is representative of the population of England as determined by comparing the HCS with the national Health Survey for England. It is not clear why the effects of sharing a bedroom on RF were present in women but not men. However, the epidemiology of RA is very different for men and women. Women are three times more likely to have RA than men and have a peak incidence in middle age. In contrast, men have an increasing incidence that becomes equal to that of women in later life. Previous work by our group has shown that an increased weight at 1 year is associated with RF in later life only in women (Walker-Bone K *et al*, unpublished data).

RF is strongly associated with the presence of RA in around 80% of subjects with RA. However, up to 10% of a general population may also be RF positive and the prevalence increases with age.[7] The presence of RF confers a risk of developing RA in the future that increases with increasing RF titres.[3] In addition, the immune pathology that results in RA begins many years before the clinical expressions of disease, with RF present up to 10 years before synovitis.[4] This makes RF a potential early marker of the pathogenic process in RA. We found that 16.6% of men and 11.8% of women in our study population were RF positive. The number of RF positive subjects in our study was higher than that seen in most general populations. However, our study population was aged 61–69 years and it is well known that the prevalence of RF increases with increasing age. In addition, we defined a positive RF at a lower level than diagnostic laboratories to ensure that we captured the maximum number of RF positive subjects. Other autoantibodies are also associated with RA. The presence of anti-cyclic citrullinated peptides (anti-CCP) is more specific than RF for the diagnosis of RA.[8] However, the greater specificity of anti-CCP reduces the number of positive subjects in the general population. We are currently investigating the effect of the early environment on anti-CCP antibodies in later

Table 2 Early life characteristics and RF in Hertfordshire Cohort Study women (n = 668)

		RF +ve cases	Odds ratio (95% CI)	
	Frequency	No (%)	Univariate	Mutually adjusted
Birth weight (g)				
<3175	279	31 (11.1)	1.0	1.0
3175–3629	238	28 (11.8)	1.07 (0.62 to 1.84)	1.20 (0.68 to 2.10)
>3629	151	20 (13.2)	1.22 (0.67 to 2.23)	1.48 (0.79 to 2.77)
			p = 0.81 on 2df	*p = 0.47 on 2df*
Weight at 1 year (g)				
<9185	227	20 (8.8)	1.0	
9185–9979	216	29 (13.4)	1.61 (0.88 to 2.93)	*Not included in model*
>9979	225	30 (13.3)	1.59 (0.88 to 2.90)	
			p = 0.23 on 2df	
Conditional growth				
Lowest third	227	25 (11.0)	1.0	1.0
Middle third	205	23 (11.2)	1.02 (0.56 to 1.86)	1.02 (0.55 to 1.88)
Highest third	236	31 (13.1)	1.22 (0.70 to 2.14)	1.14 (0.63 to 2.06)
			p = 0.74 on 2df	*p = 0.89 on 2df*
Social class (III–V v I–IIINM)				
I–IIINM	108	15 (13.9)	1.0	1.0
IIIM–V	523	60 (11.5)	0.80 (0.44 to 1.48)	0.93 (0.50 to 1.73)
Missing/unclassified	37	4 (10.8)	0.75 (0.23 to 2.43)	1.06 (0.32 to 3.54)
			p = 0.76 on 2df	*p = 0.95*
*Shared bedroom as child**				
No	286	46 (16.1)	1.0	1.0
Yes	379	32 (8.4)	0.48 (0.30 to 0.78)	0.55 (0.32 to 0.95)
			p = 0.003	*p = 0.03*
Birth order†				
1st	252	39 (15.5)	1.0	1.0
2nd–4th	330	32 (9.7)	0.59 (0.36 to 0.97)	0.65 (0.38 to 1.12)
⩾5th	85	8 (9.4)	0.57 (0.25 to 1.27)	0.83 (0.34 to 2.02)
			p = 0.08 on 2df	*p = 0.29 on 2df*

*Three results missing; †one result missing.

life. However, low numbers of positive subjects in a normal population may prevent an adequate statistical analysis.

Might early life hygiene also influence the likelihood of RA in adult life? The incidence and severity of adjuvant arthritis in rodents, an animal model of RA, is increased when animals are reared in a germ-free environment.[9] In addition, RA appears to be a disease of modern urbanised societies. Urbanisation in both South Africa[10] and Taiwan[11] has been associated with an increased incidence of RA. In addition, recent work has suggested that subjects with RA have an increased birth weight[2] and increased weight at 1 year (Walker-Bone *et al*, unpublished data), both markers of good health and perhaps better hygiene.

Parallels exist between an effect of hygiene on RF production and the effect of hygiene on allergy and asthma. The increasing prevalence of allergy has been explained by the ''hygiene hypothesis'', in which decreased infectious exposure is associated with increased allergy in the developed world.[12] It had seemed unlikely that autoimmune and allergic diseases could be influenced in a similar way by infection. The predominantly Th2 cytokine driven allergic diseases and the Th1 cytokine driven autoimmune diseases were believed to be mutually exclusive. However, epidemiological evidence has now shown that autoimmune diseases such as type I diabetes are more likely in subjects exposed to a ''cleaner'' environment during childhood[5] and that atopy has an increased incidence in subjects with autoimmune diseases, including RA.[13]

The developing immune system may be particularly vulnerable to manipulation by external factors at certain critical periods. Factors in early life can produce longlasting effects on the immune system. In humans intrauterine growth restriction results in enduring effects on immunity, including a diminished response to recall antigens.[14]

This work suggests a link between early environmental factors and the presence of the autoantibody RF in adults. It appears that a developing immune system exposed to fewer infectious micro-organisms through improved standards of hygiene may be more likely to produce RF and perhaps begin the pathological process that leads to RA.

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